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(54) **Pharmaceutical compositions and their use in the treatment of glaucoma.**

(57) New pharmaceutical compositions and their use in the treatment of glaucoma. Said compositions contain 1-moprolol as active ingredient.

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"PHARMACEUTICAL COMPOSITIONS AND THEIR USE IN THE TREATMENT OF GLAUCOMA"

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This invention relates to new pharmaceutical compositions and to their use in the treatment of glaucoma.

More particularly this invention relates to new pharmaceutical compositions containing l-moprolol as active ingredient.

l-moprolol (LEVOTENSIN® - Simes) is a drug useful in the therapy of arterial hypertension as well as in the treatment and in the prevention of coronary insufficiency.

Now it has been surprisingly found that l-moproplol shows an intraocular hypotensive effect equivalent to that of Pilocarpine and Timolol without causing those side effects and inconveniences which are inherent to Pilocarpine (myosis) and to Timolol (bradychardia, local anesthesia and tachyphylaxis).

It is known that a drug is able to exhert an intraocular hypotensive effect when it is vasoactive at the level of ciliary body in reducing the production of aqueous humour.

In addition the drug must be well tolerated locally when instilled and it must be able to pass through the intraocular structure to reach the ciliary body. Furthermore, the vascular properties of the drug must be exherted at local level without causing any systemic effect.

Therefore, the most appropppriate tests to evaluate the intraocular effects of a drug are the followings:

- effect of the drug administered locally on the normal intraocular pressure,
- evaluation of the entity and duration of the intraocular hypotensive effect of the drug on experimentally induced intraocular hypertension,

- local tolerability of the drug (biomicroscopy examination of the anterior segment, keratoesthesia, tear secretion: 15 days treatment; observation every 72 hours),
- possible cardiovascular effects after drug instillation,
- involvement of the ocular circulation in the systemic vascular phenomenon induced by intravenous administration of the drug: examination of the effect on both the systemic arterial pressure and the intraocular pressure recorded constantly and simultaneously,
- vasomotor activity of the drug on the ciliary body: correlation among vascular activity, vascular permeability and production of aqueous humour,
- comparison of the intraocular hypotensive effect of the drug with respect to the most active anti-glaucoma agents (administered at least after 48 hours one from the other),
- evaluation of the local anesthetic effect "in vitro" on the eye of cat isolated together with a substantial portion of the optical nerve and with the ciliary nerves up to the ciliary ganglion. The system is plunged into a Krebs solution and a ciliary nerve branch connected with a recorder. The cornea is submitted to light mechanical percussions and the responses of the ciliary nerve recorded either when the system is plunged into a Krebs solution or into a medicated solution,
- tachyphylaxis evaluation by administering the drug twice a day for a 30 day period in experimentally induced ocular hypertension and measuring the ocular pressure every two days at different hours.

In these tests l-moprolol has shown a remarkable hypotonic effect without showing any appreciable local or systemic side

effect.

The pharmaceutical preparations useful to the purpose are those commonly used in the ophthalmic field such as, for example, collyria or ointments.

These preparations contain a suitable amount of l-moprolol or of a pharmaceutically acceptable acid addition salt thereof together with diluents, preservatives, buffers, stabilizers etc. commonly used by the artisan. In addition, they may be ready for the use or prepared extemporaneously.

Preferably these preparations contain a quantity of l-moprolol ranging from 0.1 to 20%; still more preferred forms are those containing from 1 to 8% of l-moprolol.

Examples of suitable pharmaceutical forms are

1. Powder: a) l-moprolol 0.100 g
   sodium chloride 0.060 g
   b) l-moprolol 0.200 g
   sodium chloride 0.030 g

each of the above powders is taken up, at the time of use, with the following

Solvent: benzalkonium chloride 0.001 g - disodium EDTA 0.001 g - disodium phosphate $12H_2O$ 0.0243 g - monosodium phosphate H_2O 0.0074 g - distilled water q.s. to 10 ml.

2. Solution

l-moprolol (as hydrochloride salt)	0.500 g
sodium chloride	0.880
benzalkonium chloride	0.010
monosodium phosphate monohydrate	0.180
disodium phosphate dihydrate	0.220
distilled water	q.s. to 100 ml

3. Solution

l-moprolol (as hydrochloride salt)	4.00 g
sodium chloride	0.030 g
benzalkonium chloride	0.010 g
monosodium phosphate monohydrate	0.180 g
disodium phosphate dihydrate	0.220 g
distilled water	q.s. to 100 ml

4. Ointment

l-moprolol (as hydrochloride salt)	1.00 g
paraffin oil	25.50 g
White vaseline	73.50 g

The pharmacological activity of these collyria has been tested as follows:

- experimental animal: rabbit;
- measurement of intraocular pressure by an electronic tonometer (Mackay-Marg) after local anesthesia with 0.4% Novesine Wander;
- experimentally induced hypertension: introduction in the anterior chamber of powder of Laminaria digitata (Priestley et al., Bollettino di Oculista, 47, (10), (1968), 652-668);
- measurement of systemic arterial pressure: after isolation under local anesthesia with 1% Scurocaine,the femoral artery was cannulated by a polyvinyl catheter and the system connected with an electromanometer (Telco Thomson) and with a Varian C -2000 apparatus to record continously and graphically the arterial pressure;
- measurement of vasomotor activity on the ciliary body by a technique based on the indirect evaluation of the ciliary permeability after paracentesis (Virno et al., Bolletino di Oculistica, 58, (1982), Supplemento al N. 11-12);

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The results of the above mentioned tests have been the followings:

- l-moprolol exhibits a remarkable hypotensive effect either on the normal eye (Fig. 1) or, particularly, on the eye with experimentally induced ocular hypertension (Fig. 2);
- the biomicroscopic examination did not show significant alterations of cornea and conjunctiva neither after single instillation or after administration twice a day for 30 days;
- the instillation of the drug did not cause systemic effects;
- the intravenous administration caused a reduction of the intraocular pressure concomitant with the systemic hypotension, which means a passive partecipation of the intraocular circulation to the general vascular phenomenon (Fig. 3);
- the instillation of the compound under examination caused a response of the ciliary body which resulted in a vasodilatation when was lacking the extracirculatory pressure whereas when this pressure was present the vasodilatation phenomenon has been reversed in a "passive" vasocostriction with concomitant reduction of the vasal permeability and of the production of aqueous humour (Virno et al., Bollettino di oculistica, 58, (1982), Suppl.to No. 11-12) (Fig. 4);
- the tachyphylaxis evaluation showed that the amount of the intra-ocular hypotensive response is not reduced during the period of treatment (30 days) (Fig. 5)

The above mentioned properties have been confirmed in humans; 20 patients suffering from simple cronic glaucoma have been treated 2-3 times a day with 1/2 drops (0.5/1 mg) of collyrium containing 1% l-moprolol. Treatment caused reduction of the intraocular pressure and the preparation resulted very well tolerated: no evidence of burnings or of side effects on the

cornea. No heart rate or arterial pressure variation has been observed (Fig. 7).

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CLAIMS

1. An ophthalmic pharmaceutical composition for treating glaucoma comprising an effective amount of l-moprolol or of a pharmaceutically acceptable acid addition salt thereof.

2. An ophthalmic pharmaceutical composition according to claim 1, comprising from 1 to 8% of l-moprolol.

3. A process for treating glaucoma comprising administering locally from 0.5 to 6 mg of l-moprolol per day.

4. A process according to claim 3, where the daily administrations range from 1 to 4.

Figure 1

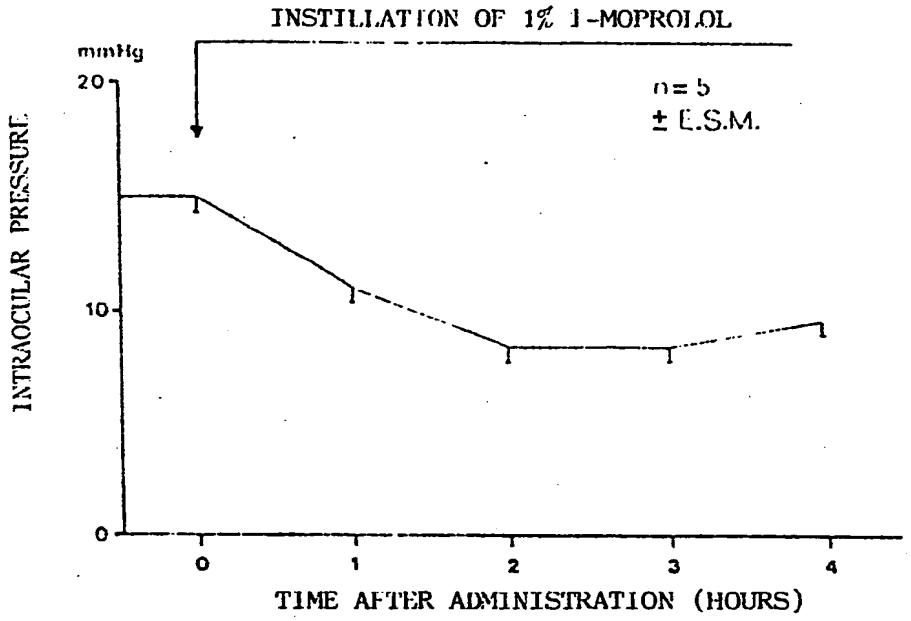


Figure 2

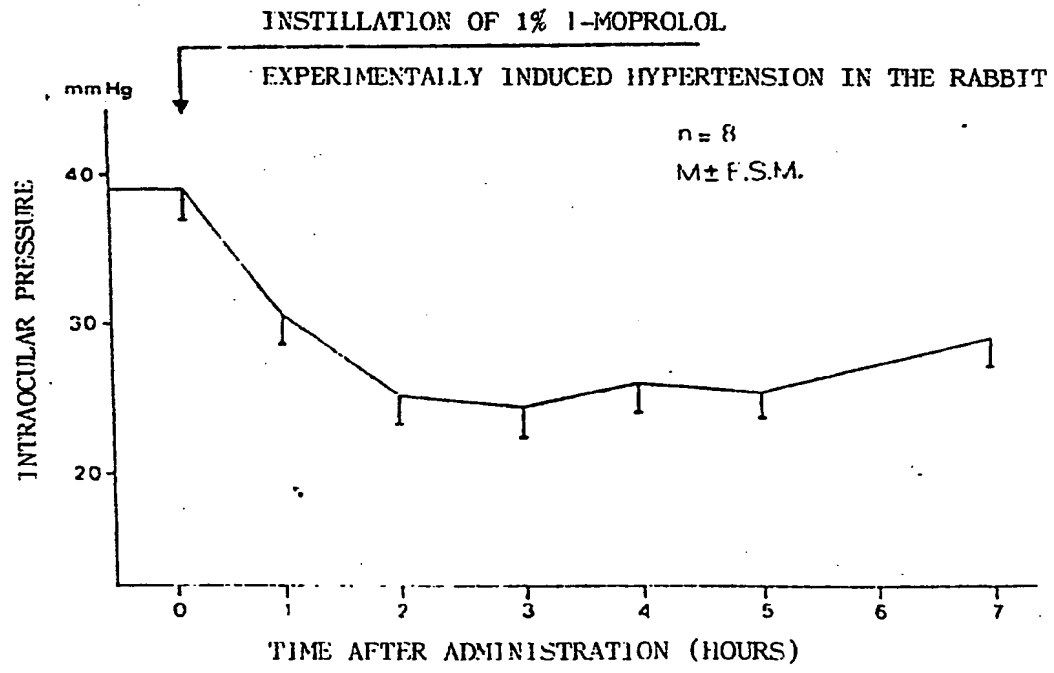


Figure 3

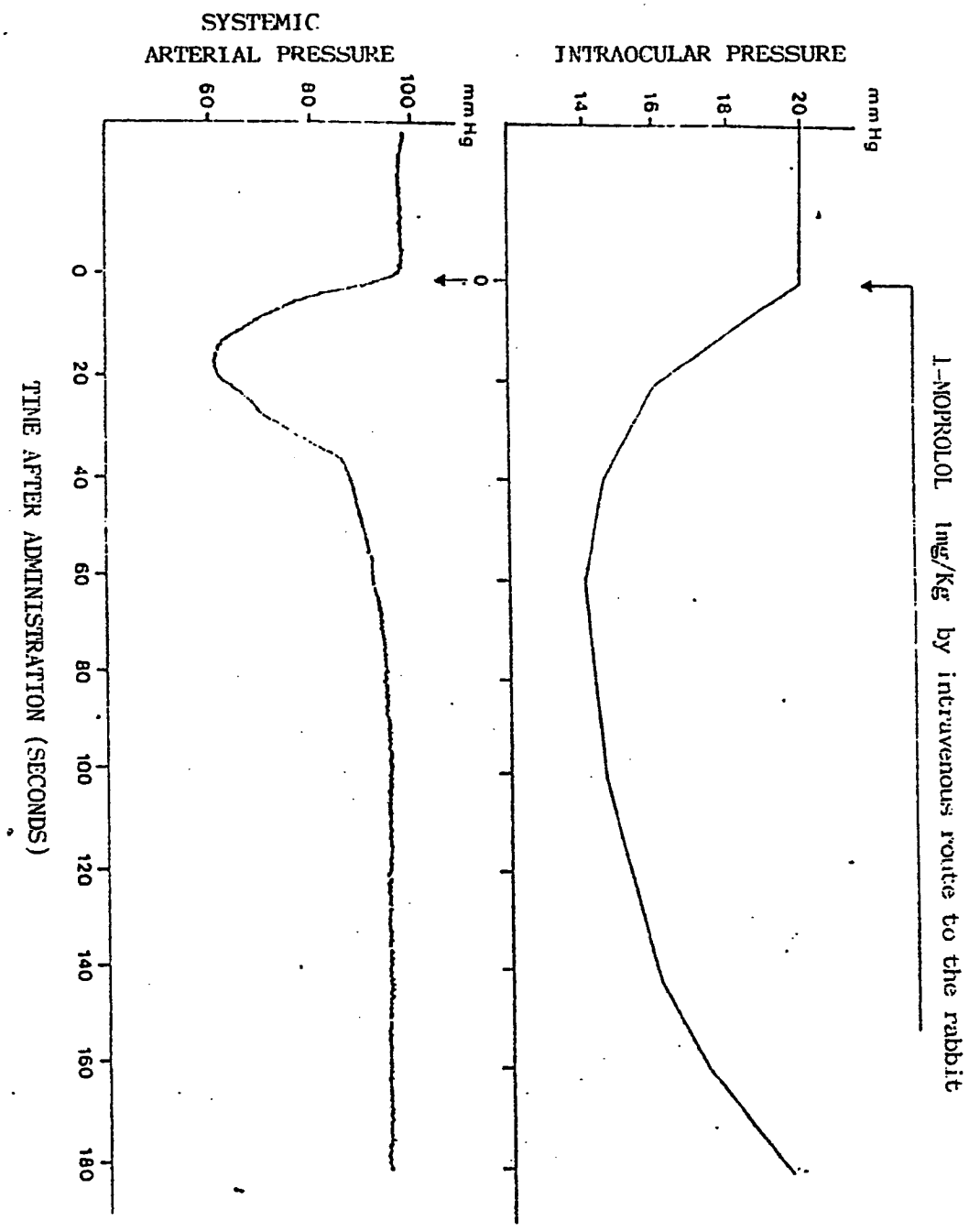
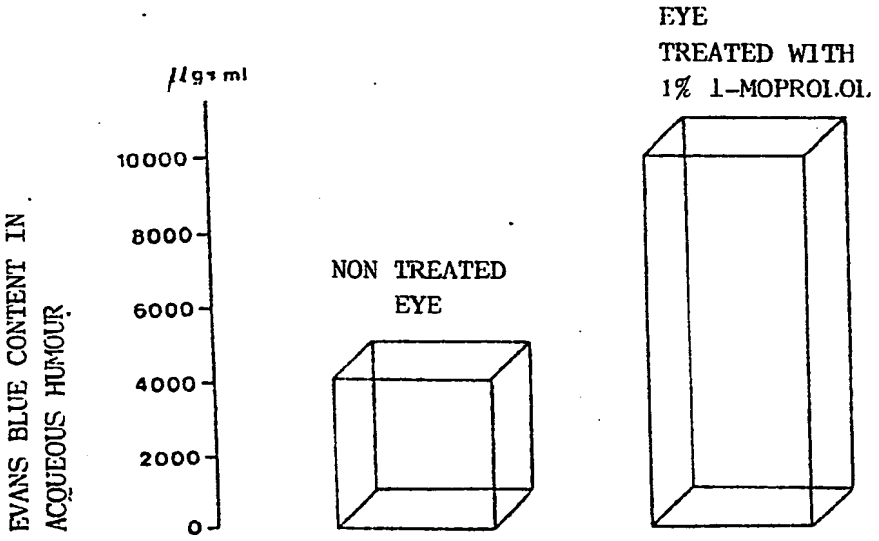

SYSTEMIC
ARTERIAL PRESSURE
INTRAOCULAR PRESSURE
mm Hg
60
80
100
14
16
18
20
0
0
20
40
60
80
100
120
140
160
180
TIME AFTER ADMINISTRATION (SECONDS)
L-MOPROLOL 1mg/Kg by intravenous route to the rabbit

Figure 4



VASOMOTOR ACTIVITY OF 1-MOPROLOL ON CILIARY CIRCULATION EVALUATED THROUGH THE ALTERATION OF THE BLOOD/AQUEOUS HUMOUR BARRIER PERMEABILITY

Figure 5

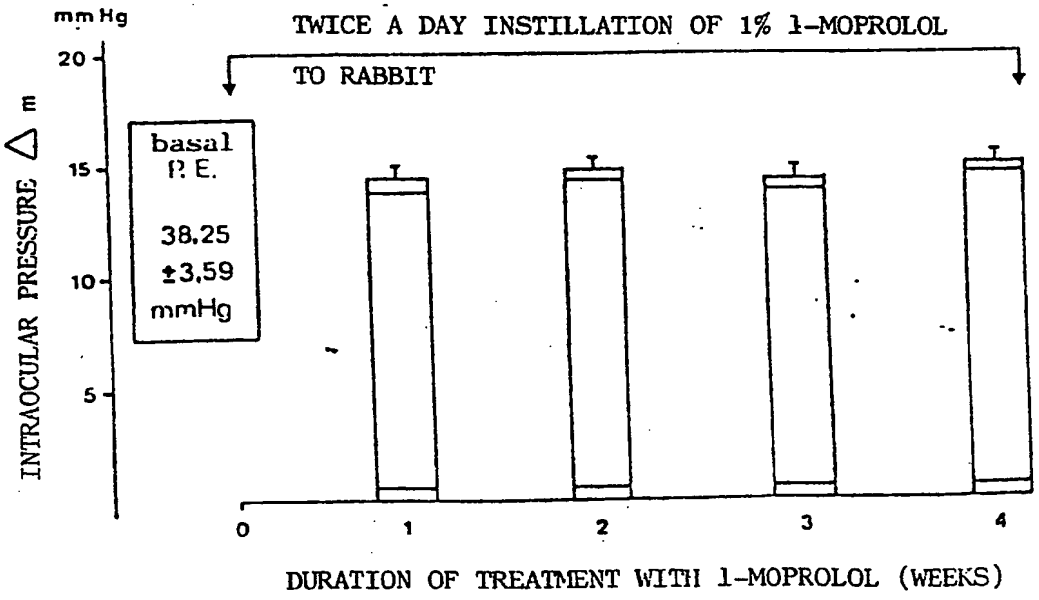


Figure 6

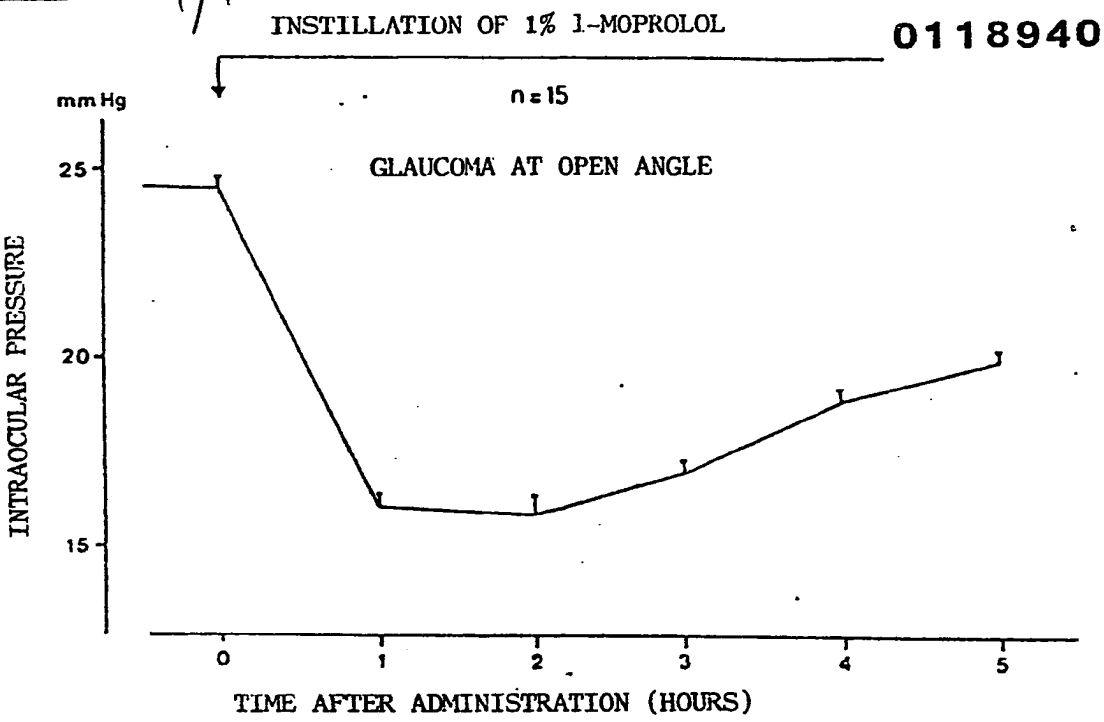
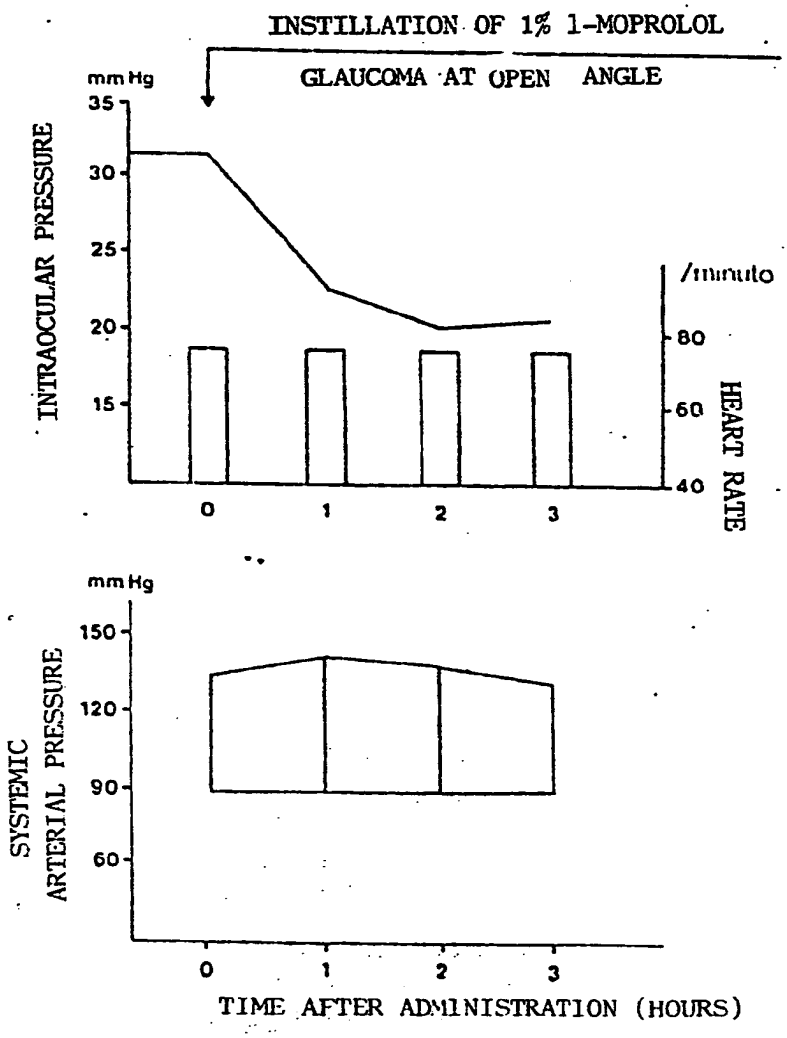


Figure 7



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EUROPEAN SEARCH REPORT

0118940
Application number

EP 84 20 0182

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
X	BE-A- 678 902 (SHELL) * Page 4, claims *	1	A 61 K 31/13
X	US-A-4 303 637 (J.W. SHELL et al.) * Claims *	1-4	
A	US-A-4 342 783 (P.L. MORSELLI et al.) * Claims *	1-4	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	18-05-1984	MOREAU J.M.

CATEGORY OF CITED DOCUMENTS

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